REMARKS

THE AMENDMENTS

Applicants cancel claims 1 to 5 and 57, and add new claims 82 to 121. These new claims add no new subject matter and are fully supported throughout the specification and the claims as filed. For the convenience of the Examiner, a marked up copy of the new claims are provided as Attachment A. Support and reasoning for the amendments are provided below.

Support for New Claims and Reasons for Amendments

These amendments are made to clarify the claims in order to expedite allowance of the present application. These claims add no new subject matter and are fully supported throughout the specification, including the drawings and the claims as originally filed.

New independent claims 82, 97, 101, and 108 refer to "a probe-survey population mixture of nucleic acid molecules that comprises one or more probes hybridized to one or more survey population nucleic acid molecules". Support for "a probe-survey population mixture of nucleic acid molecules that comprises one or more probes hybridized to one or more survey population nucleic acid molecules" can be found throughout the specification as originally filed.

For example, the figures and the Brief Description of the Figures, particularly the descriptions of FIG. 3, FIG. 7A, and FIG. 7B, refer to a probe-survey population mixture of nucleic acid molecules that comprises one or more probes hybridized to one or more survey nucleic acid molecules. The specification also describes the hybridization of one or more probes to one or more survey population molecules, for example, in the section HYBRIDIZATION OF PROBE AND SURVEY POPULATION that begins on page 43, line 17 and continues through page 44, line 15.

The use of "at least one probe that comprises a known or suspected SNP or mutation" in the methods of the present invention, recited in new independent claim 82, is referred to in the text and in figures 6A, 6B, 7A, 7B, and 8. For example, in describing embodiments of the present invention, on page 26, lines 1-3, the specification reads: "In this embodiment, the probe nucleic acid molecules include DNA

sequences that include a known or suspected SNP, where the known or suspected mutation or SNP is not at the terminus of the probe nucleic acid molecules." On page 27, lines 13-16, the specification reads "In this embodiment, the probe nucleic acid molecules include DNA sequences that include known or suspected mutation or SNP sites, where the known or suspected mutation or SNP site is not at the termini of the probe nucleic acid molecules." On page 29, lines 4-6 the specification reads "The set of probe nucleic acid molecules terminate at a known or suspected mutation or SNP site, and the nucleotide at the known or suspected mutation or SNP site is labeled." Thus, the specification describes probes that comprise SNPs or mutations at their termini, as well as probes that comprise SNPs or mutations that are not at the termini of the probes, as recited in new dependent claims 85 and 86. In support of new dependent claim 87, the definition of "probe" states (page 8, lines 16-18, and again on page 32, lines 15 and 16)) that a probe can be RNA, DNA, or a combination of both RNA and DNA."

Further, a section of the specification on probe nucleic acid molecules reads: "Preferably, the portions of the probe nucleic acid molecule that are identical or substantially identical to an attached nucleic acid molecule and that are not identical or substantially identical to an attached nucleic acid molecule are adjacent. Preferably, the border between the identical and non-identical portions is a known or suspected mutation or SNP." Finally, in Example II, the use of a probe that comprises an SNP at position 13 (SEQ ID NO:4) in the methods of the present invention is described. The sequence of the probe is given on page 67, line 12 (attached nucleic acid sequences that are partially complementary and vary at this position.are given on page 67, line 24 through page 68, line 3.)

The specification also states on page 38, lines 4 and 5: "The survey population of nucleic acid molecules can be comprised of RNA, of DNA, or of a combination of DNA and RNA" in support of new dependent claims 83 and 84.

In support of the use of nucleases, which are distinct from proteases, recited in new dependent claims 88, 89, and 90, the specification states on page 44:

> The probe nucleic acid molecule-survey population nucleic acid molecule mixture of the present invention can be treated with one or more nucleolytic activities. Nucleolytic activities of the present invention can be chemical cleavage agents, such as osmium tetroxide, hydrogen peroxide, hydroxylamine, and permanganate, or can be enzymes such as nucleases. Preferred nucleases include single-strand specific nucleases, such as S1 nuclease, Mung Bean Nuclease, Rnase T1, Rnase A, or Rnase H.

Compositions and formats for solid supports, recited in new claims 91 and 92, are described in the specification on page 42, line 17 through page 43, line 16. In particular:

> A solid support of the present invention is a solid material having a surface for attachment of molecules, compounds, cells, or other entities. A solid support can be a membrane, such as, for example, a nylon or nitrocellulose membrane, or can be a plate or dish and can be comprised of glass, ceramics, metals, or plastics, such as, for example, a 96-well plate made of, for example, polystyrene, polypropylene, polycarbonate, or polyallomer. A solid support can also be a particle or bead that can comprise glass, can comprise one or more plastics or polymers, such as, for example, polystyrene, polyacrylamide, sepaharose, agarose, cellulose or dextran, and/or can comprise metals, particularly paramagnetic metals, such as iron.
>
> One preferred solid support of the present invention is a chip or array that comprises a flat surface, and that may comprise glass, silicon, nylon, polymers, plastics, ceramics, or metals.

In support of new dependent claims 93 and 94, the specification reads on page 39 line27 to page 40 line 3: "One or more attached nucleic acid molecules of the present invention is preferably at least partially complementary, or at least partially substantially complementary, or at least partially identical, or at least partially substantially identical, to at least one probe nucleic acid molecule of the present invention." The use of atttached nucleic acid molecules complementary to a probe nucleic acid is further described on page 29 lines 9 to 13:

> In this embodiment, the probes are at least partially complementary or at least partially substantially complementary to the attached nucleic acid molecules that are bound to the array, and are at least partially complementary or at least partially substantially complementary to at least one nucleic acid molecule of the survey population.

Support for an attached nucleic acid molecule having a mutation or SNP at its unattached 3' terminus (claim 94) occurs on page 25, line 23 to page 26, line 3:

> A set of attached nucleic acid molecules is also provided, in which the attached nucleic acid molecules are bound to a solid support in the form of an array, and in which the attached nucleic acid molecules are DNA oligonucleotides that are partially complementary to the probe nucleic acid molecules. The 3' ends of the attached nucleic acid molecules are unattached, and the 3' termini of attached nucleic acid molecules are known or suspected SNP sites.

Labeling attached nucleic acid molecule/nucleolytic activity-protected nucleic acid molecule complexes with at least one detectable label (new claim 95) is described in several passages of the application. For example, a passage on page 29 (lines 4-6) reads: "The set of probe nucleic acid molecules terminate at a known or suspected mutation or SNP site, and the nucleotide at the known or suspected mutation or SNP site is labeled.", and further down in the same paragraph (on pages 29, line 25 to page 30, line 2):

> "If a probe sequence at a known or suspected mutation or SNP site is complementary to a sequence in the survey population, the labeled SNP nucleotide will remain on a probe nucleic acid molecule. Following nuclease treatment, the nuclease is inactivated, for example by addition of EDTA. The protected survey population nucleic acid molecules are removed, for example by digestion with RNAse, and the probe nucleic acid molecules are hybridized to the array. A positive signal on the array is indicative of a particular nucleotide at the site of the known or suspected SNP or mutation in a nucleic acid of the survey population.

Further, on page 26, line 21 through page 27, line 2, the specification reads:

> The array is treated with a polymerase, such as the MMLV reverse transcriptase, and labeled nucleotides. The polymerase extends the attached nucleic acid molecule using the protected nucleic acid molecule (in this instance, the protected RNA survey population nucleic acid molecule) as a template only if there is complementarity between the protected RNA fragment and the attached nucleic acid molecule at the mutation or SNP site. After washing the array, the array is scanned. *Incorporation of label at a position on the array is indicative of precise complementarity between the attached nucleic acid molecule and the protected RNA molecule at the SNP site, and thus identifies the sequence at an SNP site in an expressed gene.* [emphasis added]

On pages 28 (beginning at line 18) and 29 (lines 1 and 2), the specification also states:

> The array is treated with a DNA polymerase, such as the Klenow fragment, and labeled nucleotides. The polymerase extends the attached nucleic acid molecule using the protected nucleic acid molecule (in this embodiment, the protected survey population nucleic acid molecule) as a template only if there is complementarity between the protected survey population fragment and the attached nucleic acid molecule at the mutation or SNP site. Extension of the protected nucleic acid molecule using the attached nucleic acid molecule as a primer, which can lead to false positives, can be prevented by designing the entire attached nucleic acid molecule (with the exception of the SNP site) to be complementary to a portion of the protected survey population nucleic acid molecule. After washing the array, the array is scanned. *Incorporation of label at a position on the array is indicative of precise complementarity between the attached nucleic acid molecule and the protected DNA molecule of the survey population at the SNP site, and thus identifies the sequence at a mutation or SNP site in a gene.*[emphasis added]

Support for "contacting said population of nucleolytic activity-protected nucleic acid molecules with one or more particles comprising one or more attached nucleic acid molecules", as cited in new independent claim 97 is found in the definition of "attached nucleic acid molecule" on page 12, lines 12 and 13, which states "An "attached nucleic acid molecule" is a nucleic acid molecule that is bound to a solid support", and in the definition of "solid support" provided on page 15, lines 3-9. The specification states on page 42, lines 21-24, that "A solid support can also be a particle or bead that can comprise glass, can comprise one or more plastics or polymers, such as, for example, polystyrene, polyacrylamide, sepaharose, agarose, cellulose or dextran, and/or can comprise metals, particularly paramagnetic metals, such as iron." (In support of new claims 98, 99, and 100). The specification also states on page 43:

> Another preferred solid support of the present invention is a particle that comprises a spherical or nonflat surface, and that may comprise glass, polymers (such as, but not limited to, polyacrylamide, agaroses, dextrans, cellulose, or plastics), ceramics, or metals. Nucleic acid molecules can be attached to the particles, which may or may not be porous. Such particles can be used, for example, to capture nucleic acid molecules of the survey population or probe nucleic acid molecules by hybridization.

Support for amplifying said population of nucleolytic activity-protected nucleic acid molecules, recited in new claim 101, can be found on page 45, lines 18-26:

> In some embodiments of the present invention, it may be desirable to amplify nucleolytic-activity protected nucleic acid molecules. Such embodiments include embodiments directed toward the detection of contaminants or pathogens. Methods of DNA amplification are well known in the art. Amplification of RNA is known in the art as well, and generally relies on a first cDNA synthesis reaction using a reverse transcriptase. Preferably, the amplification of nucleolytic-activity protected products is linear or substantially linear, and preferably, the amplification preferentially amplifies one strand, preferably the strand that is at least partially complementary, or at least partially substantially complementary to one or more attached nucleic acid molecules of the present invention.

The specification also reads on page 31, lines 10-16:

> Alternatively, the probe does not comprise a specific binding member such as biotin, and after nuclease treatment and inactivation of the nuclease, protected survey nucleic acid molecules can be amplified. Preferably, amplification reactions amplify only the survey nucleic acid molecule and not the probe nucleic acid. This can be accomplished, for example, by including in the amplification reactions one or more primers that are complementary or substantially complementary to at least a portion of the survey population nucleic acid molecules, and by not including in the amplification reactions primers that are complementary or substantially complementary to at least a portion of one or more probe nucleic acid molecules.

Labeling said attached nucleic acid molecule/nucleolytic activity-protected nucleic acid molecule complexes with at least one detectable label using at least one polymerase, recited in new independent claim 108, can be found in several places in the application. It is described extensively in a section beginning on page 47, line 14 that extends through line 25 of page 51.

The use polymerase for labeling complexes hybridized to a solid support is also described in the context of specific embodiments, for example on page 19, lines 14-21:

> After washing to remove unhybridized nucleic acid molecules, the array is treated with a DNA polymerase, such as the Klenow fragment of *E. coli* DNA polymerase, and labeled nucleotides. The DNA polymerase extends an attached nucleic acid molecule using a protected nucleic acid molecule (in this embodiment, the protected probe nucleic acid molecules) as a template by incorporating labeled nucleotides.;

on page 20, lines 19-23:

> After washing to remove unhybridized nucleic acid molecules, the array is treated with a RNA-dependent DNA polymerase, such as MMLV reverse transcriptase, and labeled nucleotides. The reverse transcriptase extends the attached nucleic acid molecule using the protected nucleic acid molecule (in this instance, the survey population RNA fragments) as templates by incorporating labeled nucleotides.;

on page 26, lines 21-26:

> The array is treated with a polymerase, such as the MMLV reverse transcriptase, and labeled nucleotides. The polymerase extends the attached nucleic acid molecule using the protected nucleic acid molecule (in this instance, the protected RNA survey population nucleic acid molecule) as a template only if there is complementarity between the protected RNA fragment and the attached nucleic acid molecule at the mutation or SNP site. ;

and on page 28, lines 17-25:

> The array is treated with a DNA polymerase, such as the Klenow fragment, and labeled nucleotides. The polymerase extends the attached nucleic acid molecule using the protected nucleic acid molecule (in this embodiment, the protected survey population nucleic acid molecule) as a template only if there is complementarity between the protected survey population fragment and the attached nucleic acid molecule at the mutation or SNP site. Extension of the protected nucleic acid molecule using the attached nucleic acid molecule as a primer, which can lead to false positives, can be prevented by designing the entire attached nucleic acid molecule (with the exception of the SNP site) to be complementary to a portion of the protected survey population nucleic acid molecule.

Depictions of embodiments in which labeling of hybiridized complexes uses a polymerase can also be found in figures 1A, 1B, 6A, and 6B.

PRIORITY

Applicants will supply a certified copy of an application filed in Peoples' Republic of China on August 24, 2000 at a later date after allowable subject matter is established.

OATH/DECLARATION

Applicants will supply a new oath at a later date.

DRAWINGS

Applicants provide proposed drawings that address the changes margins of the Figures 3, 6A, 6B and 8 as set forth in FORM PTO-948.

SEQUENCE RULES COMPLIANCE

Applicants' respectfully acknowledge that the application has complied with Requirement for Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

INFORMATION DISCLOSURE STATEMENT

Applicants' have submitted an Information Disclosure Statement, Form 1449, and copies of cited references, in two previous submissions. Also, filed herewith is the submission of a third Information Disclosure Statement.

SPECIFICATION

A brief description of the drawings was provided on pages 4-6 of the filed application.

Applicants have also provided a Submission of Proposed Abstract with this response..

INTERVIEW

Applicant's representative, David R. Preston, thanks the Examiner for the courteous and informative telephonic interview of July 16, 2002. During that interview, the sum and substance of the claims and comments provided in this response were generally discussed.

APPLICANTS' CLAIMED INVENTION IS NOT INDEFINITE UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Hybridization of Probe and Survey Population

Applicants do not agree that claim 1 is vague and indefinite over step (a) for failure to state whether a probe-survey population mixture of nucleic acid molecules is a hybridized complex of at least one probe nucleic acid molecule and a survey population of nucleic acid molecules or not. However, applicants have submitted new independent claims 82, 97, 101, and 108 that include the phrase "that comprises one or more probe nucleic acid molecules hybridized to one or more survey population nucleic acid molecules" for clarity to expedite prosecution of the claims.

The specification indicates that a probe-survey population mixture of nucleic acid molecules can comprise one or more probe nucleic acid molecules hybridized to one or more survey population nucleic acid molecules. This is detailed in the description under the heading 'HYBRIDIZATION OF PROBE AND SURVEY POPULATION' that states "The method of the present invention includes hybridization of one or more probe nucleic acid molecules of the present invention with a survey population of nucleic acid molecules." (p.43, lines 18-19) and later in the same section: "The hybridization reaction can be done with both probe nucleic acid molecules and survey nucleic acid molecules in solution, under conditions that

promote hybridization between molecules that are complementary, partially complementary, substantially complementary, or partially substantially complementary." (p. 43, lines 24-27). Further along in the same section, the specification reads: "Contacting one or more probe nucleic acid molecules of the present invention with a survey population of nucleic acid molecules under conditions that promote hybridization between nucleic acid molecules that are at least partially complementary or substantially complementary results in a probe-survey population mixture of nucleic acid molecules. The probe-survey population mixture of nucleic acid molecules can include single-stranded nucleic acid molecules, double-stranded nucleic acid molecules, and/or nucleic acid molecules that are partially single-stranded and partially double-stranded." (p.44, lines 12-15). Thus, a probe-survey population mixture of nucleic acid molecules comprises one or more probe nucleic acid molecules hybridized to one or more survey population molecules.

It is also noted that in an earlier section of the description under the heading 'PROBE NUCLEIC ACID MOLECULES' the specification states (p. 33, line 19 through page 34, line 6):

> At least one of the probe nucleic acid molecules of the present invention is
>
> preferably at least partially complementary, or at least partially substantially complementary, to one or more nucleic acid molecules that are known to be present or are suspected of being present in a survey population of nucleic acids. Probe nucleic acid molecules of the present invention are preferably at least partially single-stranded. Preferably, at least a portion of a probe nucleic acid molecule that is complementary to a nucleic acid molecule that is known to be or suspected of being present in the survey population is provided in the single-stranded state. Double-stranded nucleic acid molecules may be converted to the single-stranded or partially single-stranded state for use as probes, for example by denaturation of double-stranded molecules, or by treatment of the double-stranded nucleic acid molecules with nucleases or polymerases. Preferably, at least one of the nucleoside linkages in a probe nucleic acid molecule is sensitive to cleavage by a nucleolytic agent when the probe nucleic acid molecule or portion thereof is in the single stranded state, but is not sensitive to cleavage by a nucleolytic agent when the probe nucleic acid molecule is in the double stranded state, *such as when hybridized to a nucleic acid molecule that is at least partially complementary or at least partially substantially complementary.* [Emphasis added.]

The formation of hybrids between probe nucleic acid molecules and nucleic acid molecules of the survey population in a probe-survey population mixture of nucleic acid molecules is also found in the Brief Description of the Figures:

> **FIG. 3** depicts one aspect of the present invention, in which two survey populations of RNA are separately hybridized to sets of labeled probe nucleic acid molecules, where the set of probe nucleic acid molecules hybridizing to the first survey population carries a different label than the set of probe nucleic acid molecules hybridizing to the second survey population, and the nucleolytic activity-protected probe molecules are hybridized to the same array. (p.4, line 24-p.5, line2)
>
> **FIG. 7A** depicts one aspect of the present invention, in which mutations or SNPs are detected by hybridization of an end-labeled DNA probe to a survey population of RNA molecules from normal cells, followed by nuclease treatment and hybridization of the probe to an array.(p.5, lines 18-21)
>
> **FIG. 7B** depicts one aspect of the present invention, in which mutations or SNPs are detected by hybridization of an end-labeled DNA probe to a survey population of RNA molecules from abnormal cells, followed by nuclease treatment and hybridization of the probe to an array. (P.5, lines 22-25)

In addition, all of the submitted figures (Figure 1A, Figure 1B, Figure 2, Figure 3, Figure 4, Figure 5, Figure 6, Figure 7A, Figure 7B, and Figure 8) depict probe nucleic acid molecules hybridized to survey population nucleic acid molecules.

Thus, new claims 81, 97, 101, and 108 are definite under 35 §USC 112, second paragraph. Accordingly, Applicants request that this rejection be withdrawn.

Treating said probe-survey population mixture of nucleic acid molecules with a nucleolytic activity

Applicants do not agree that the phrase "treating said probe-survey population mixture of nucleic acid molecules with a nucleolytic activity" used in new independent claims 81, 97, 101, and 108 is vague and indefinite. On page 12 of the application, lines 4-9, a definition for "nucleolytic activity "is provided:

> A "nucleolytic activity" or "nucleolytic agent" is an activity that can cleave nucleosidic bonds to degrade nucleic acid molecules. Nucleolytic activities or agents can be enzymes, such as, for example, Dnase I, Exonuclease III, Mung Bean Nuclease, S1 Nuclease, RNAse H, or Rnase A, or can be chemical compounds, such as hydrogen peroxide, osmium tetroxide, hydroxylamine, or potassium permanganate, or can be chemical conditions, such as high or low pH.

In addition, a section under the heading TREATMENT WITH NUCLEOLYTIC ACTIVITY, beginning on page 44, line 16, and extending to line 19 on page 46, describes conditions that can be used in the methods of the present invention, such as digestion with nucleases or use of chemical cleavage agents. Thus, the claims are definite under 35 §USC 112, second paragraph. Applicants therefore request that the rejection be withdrawn.

Nucleolytic activity-protected nucleic acid molecules

Applicants do not agree that the phrase "nucleolytic activity-protected nucleic acid molecules" used in new claims 81, 97, 101, and 108 is vague and indefinite. "Nucleolytic activity-protected nucleic acid molecules" are defined on page 13, lines 8-23:

> A "nucleolytic activity-protected nucleic acid molecule" is at least one nucleic acid molecule that has been treated with one or more nucleolytic activities, and that has not been degraded by the nucleolytic activities. A nucleolytic activity protected nucleic acid molecule can be single-stranded or may be double-stranded, or may be partially single-stranded and partially double-stranded. A nucleolytic activity-protected nucleic acid molecule can be resistant to one or more nucleolytic activities. Resistance to nucleolytic activities can be conferred, for example, by conformation of a nucleic acid molecule when it was treated with a nucleolytic activity (including being in the double-stranded state), by the nucleotide sequence of a nucleic acid molecule, or by one or more nucleoside linkages of a nucleic acid molecule. A nucleolytic activity-protected nucleic acid molecule can be a

> nucleolytic activity-protected survey population nucleic acid molecule or fragment thereof, or a nucleolytic activity-protected probe nucleic acid molecule or fragment thereof, or can comprise all or portions of both survey population nucleic acid molecules and probe nucleic acid molecules. In addition, in some embodiments, attached nucleic acid molecules or portions thereof can be nucleolytic activity-protected nucleic acid molecules. Nucleolytic activity-protected nucleic acid molecules can include or be operably linked to other compounds as well, for example, peptides, chemical moieties, and/or labels.

Note, also, as quoted above, the applications definition for nucleolytic activity. Nucleolytic activity is used in the art to denote activities that degrade nucleic acids, and generally not used to refer to proteolytic activity. Thus, the claims are definite under 35 §USC 112, second paragraph, and applicants request that the rejection be withdrawn.

Nucleolytic activity-sensitive nucleic acid molecules

The phrase "nucleolytic activity-sensitive nucleic acid molecules" used in new claims 81, 97, 101, and 108, is used on page 45, lines7-17 to denote molecules that can be degraded by a nucleolytic activity:

> Treatment with a nucleolytic activity removes nucleolytic activity-sensitive nucleic acid molecules from the probe-survey population mixture of nucleic acid molecules, resulting in a population of nucleolytic-activity-protected nucleic acid molecules. In a preferred embodiment of the present invention, treatment with a nucleolytic activity removes single-stranded nucleic acid molecules and single-stranded regions of nucleic acid molecules from the probe-survey population mixture of nucleic acid molecules, and results in a population of double-stranded nucleolytic activity-protected nucleic acid molecules. However, the present invention also contemplates that molecules may be protected from or sensitive to nucleolytic activity for reasons other than that they are double-stranded or single-stranded. For example, particular nucleic acid molecules may comprise one or more nuclease-resistant linkages that render the nucleic acid molecules or portions thereof resistant to particular nucleases.

Thus, the claims are definite under 35 §USC 112, second paragraph and applicants respectfully request that the rejection be withdrawn.

Generating a population of nucleolytic activity-protected nucleic acid molecules

Applicants do not agree that step (b) of new claims 81, 97, 101, and 108 is vague and indefinite because it is unclear how "a population of nucleolytic activity-protected nucleic acid molecules" is to be generated if said probe-survey population mixture of nucleic acid molecules is DNA or RNA while a nuclease used in the assay is a Dnase or Rnase. The specfication gives several examples of how nucleolytic activity-protected nucleic acid molecules can be obtained. For example, the definition of a nucleolytic activity-protected nucleic acid molecule on page 13 of the specification (lines 8-23) reads:

> A "nucleolytic activity-protected nucleic acid molecule" is at least one nucleic acid molecule that has been treated with one or more nucleolytic activities, and that has not been degraded by the nucleolytic activities. A nucleolytic activity protected nucleic acid molecule can be single-stranded or may be double-stranded, or may be partially single-stranded and partially double-stranded. *A nucleolytic activity-protected nucleic acid molecule can be resistant to one or more nucleolytic activities. Resistance to nucleolytic activities can be conferred, for example, by conformation of a nucleic acid molecule when it was treated with a nucleolytic activity (including being in the double-stranded state), by the nucleotide sequence of a nucleic acid molecule, or by one or more nucleoside linkages of a nucleic acid molecule.* A nucleolytic activity-protected nucleic acid molecule can be a nucleolytic activity-protected survey population nucleic acid molecule or fragment thereof, or a nucleolytic activity-protected probe nucleic acid molecule or fragment thereof, or can comprise all or portions of both survey population nucleic acid molecules and probe nucleic acid molecules. In addition, in some embodiments, attached nucleic acid molecules or portions thereof can be nucleolytic activity-protected nucleic acid molecules. Nucleolytic activity-protected nucleic acid molecules can include or be operably linked to other compounds as well, for example, peptides, chemical moieties, and/or labels. [emphasis added]

The specification further states on page 45, lines 7-17:

> Treatment with a nucleolytic activity removes nucleolytic activity-sensitive nucleic acid molecules from the probe-survey population mixture of nucleic acid molecules, resulting in a population of nucleolytic-activity-protected nucleic acid molecules. In a preferred embodiment of the present invention, treatment with a nucleolytic activity removes single-stranded nucleic acid molecules and single-stranded regions of nucleic acid molecules from the probe-survey population mixture of nucleic acid molecules, and results in a population of double-stranded nucleolytic activity-protected nucleic acid molecules. However, the present invention also contemplates that molecules may be protected from or sensitive to

nucleolytic activity for reasons other than that they are double-stranded or single-stranded. For example, particular nucleic acid molecules may comprise one or more nuclease-resistant linkages that render the nucleic acid molecules or portions thereof resistant to particular nucleases.

Thus, it is clear from the specification that nucleic acid molecules can be protected by being resistant to particular nucleases, for example, by being in the single stranded state, or by having nuclease-resistant linkages. Thus, the claims are definite under 35 §USC 112, second paragraph. Applicants therefore respectfully request that the rejection be withdrawn.

Nucleolytic activity-resistant linkages

Applicants do not agree that claim 4 is vague and indefinite over the phrase "nucleolytic activity-resistant linkages". The two passages of the specification cited in the preceding section 'Generating a population of nucleolytic activity-protected nucleic acid molecules' also describe nucleolytic activity-resistant linkages. However, applicants have requested that claim 4 be cancelled, and respectfully request that the rejection be withdrawn.

KRIS ET AL. FAILS TO ANTICIPATE APPLICANTS' INVENTION UNDER 35 U.S.C. § 102(E)

Applicants claims 1, 2, 4, 5 and 57 are not anticipated by the Kris et al. reference. To expedite the allowance of the application, however, Applicants have provided new independent claims 82, 97, 101, and 108 which are clearly distinguishable over this reference. Applicants do so without prejudice to pursuing the original claims in another application.

Kris et al. (US Patent No. 6,238,869, filed on June 21, 1999) do not teach all limitations recited in new independent claims 82, 97, 101, and 108. As to claim 82, Kris et al. do not teach or suggest the use of a probe that comprises an SNP or a mutation in methods of identifying one or more nucleic acid molecules. As to claim 97, Kris et al. do not teach or suggest the use of a particle as a solid support in methods of identifying one or more nucleic acid molecules. As to claim 101, Kris et al. do not teach or

suggest amplification of nucleolytic acitivity-protected fragments in methods of identifying one or more nucleic acid molecules. As to claim 108, Kris et al. do not teach or suggest labeling of protected complexes hybridized to a solid support using a polymerase in methods of identifying one or more nucleic acid molecules.

For the foregoing reasons, Applicants submit that the new claims cannot be anticipated by the Kris et al. reference under 35 U.S.C. § 102(e). Accordingly, Applicants respectfully request that these rejections be withdrawn.

THE CLAIMED INVENTION IS NOT OBVIOUS OVER KRIS ET AL. IN VIEW OF TYAGI ET AL., UNDER 35 U.S.C. § 103(A)

Applicants have withdrawn claim 3 to expedite the prosecution of the claims. Applicants do so without prejudice, reserving the right to prosecute such claim in further applications. Newly submitted claims do not recite a probe that is at least partially single-stranded. Therefore Applicants respectfully request that the rejection be withdrawn.

Applicants respectfully submit that the claims are ready for examination and in condition for allowance.

Respectfully submitted,

Date: July 17, 2002

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In the event this paper is deemed not timely filed the applicants hereby petition for an appropriate extension of time. The fee for this extension may be charged to Deposit Account No.501321 along with any other additional fees which may be required with respect to this paper; any overpayment should be credited to the account. If any fees charged to this Deposit Account will exceed $500, applicant respectfully requests that its counsel be notified of such amounts before the Deposit Account is charged.

ATTACHMENT A

82. A method of identifying one or more nucleic acid molecules, comprising:

a) contacting at least one probe nucleic acid molecule that comprises a known or suspected SNP or mutation with a survey population of nucleic acid molecules under conditions that promote hybridization between nucleic acid molecules to generate a probe-survey population mixture of nucleic acid molecules that comprises one or more probe nucleic acid molecules hybridized to one or more survey population nucleic acid molecules;

b) treating said probe-survey population mixture of nucleic acid molecules that comprises one or more probe nucleic acid molecules hybridized to one or more survey population nucleic acid molecules with a nucleolytic activity, such that nucleolytic activity-sensitive nucleic acid molecules are digested, to generate a population of nucleolytic activity-protected nucleic acid molecules;

c) contacting said population of nucleolytic activity-protected nucleic acid molecules with a solid support comprising one or more attached nucleic acid molecules under conditions that promote hybridization between nucleic acid molecules to generate attached nucleic acid molecule/nucleolytic activity-protected nucleic acid molecule complexes; and

d) identifying one or more of said attached nucleic acid molecules or one or more of said nucleolytic activity-protected nucleic acid molecules in one or more attached nucleic acid molecule/nucleolytic activity-protected nucleic acid molecule complexes.

83. The method of claim 82, wherein said survey population comprises RNA.

84. The method of claim 82, wherein said survey population comprises DNA.

85. The method of claim 82, wherein said known or suspected SNP or mutation is at a terminus of said probe.

86. The method of claim 82, wherein said known or suspected SNP or mutation is not at a terminus of said probe.

87. The method of claim 82, wherein said at least one probe comprises DNA.

88. The method of claim 82, wherein said nucleolytic activity comprises at least one nuclease.

89. The method of claim 88, wherein said at least one nuclease is a single-strand specific nuclease.

90. The method of claim 89, wherein said single-strand specific nuclease is S1 nuclease, Mung Bean nuclease, Rnase T1, RNAse A, or RNAse H.

91. The method of claim 82, wherein solid support comprises glass, silicon, nylon, one or more polymers, one or more plastics, one or more ceramics, or one or more metals.

92. The method of claim 91, wherein said solid support is an array.

93. The method of claim 82, wherein said one or more attached nucleic acid molecules are at least partially complementary to said at least one probe nucleic acid molecule.

94. The method of claim 82, wherein said known or suspected SNP or mutation occurs at the unattached 3' terminus of said one or more attached nucleic acid molecules.

95. The method of claim 82, wherein said identifying comprises labeling said attached nucleic acid molecule/nucleolytic activity-protected nucleic acid molecule complexes with at least one detectable label.

96. The method of claim 95, wherein said labeling uses at least one polymerase.

97. A method of identifying one or more nucleic acid molecules, comprising:

a) contacting at least one probe nucleic acid molecule with a survey population of nucleic acid molecules under conditions that promote hybridization between nucleic acid molecules to generate a probe-survey population mixture of nucleic acid molecules that comprises one or more probe nucleic acid molecules hybridized to one or more survey population nucleic acid molecules;

b) treating said probe-survey population mixture of nucleic acid molecules that comprises one or more probe nucleic acid molecules hybridized to one or more survey population nucleic acid molecules with a nucleolytic acitivity, such that nucleolytic activity-sensitive nucleic acid molecules are digested, to generate a population of nucleolytic activity-protected nucleic acid molecules;

c) contacting said population of nucleolytic activity-protected nucleic acid molecules with one or more particles comprising one or more attached nucleic acid molecules under conditions that promote hybridization between nucleic acid molecules to generate attached nucleic acid molecule/nucleolytic activity-protected nucleic acid molecule complexes; and

d) identifying one or more of said attached nucleic acid molecules or one or more of said nucleolytic activity-protected nucleic acid molecules in one or more attached nucleic acid molecule/nucleolytic activity-protected nucleic acid molecule complexes by labeling said attached nucleic acid molecule/nucleolytic activity-protected nucleic acid molecule complexes with at least one detectable label using at least one polymerase.

98. The method of claim 97, wherein said one or more particles is paramagnetic.

99. The method of claim 97, wherein said one or more particles comprises one or more polymers.

100. The method of claim 99, wherein at least one of said one or more polymers is polystyrene, polycarboate, polyvinylchloride, polypropylene, polyacrylamide, sepharose, agarose, cellulose, or dextran.

101. A method of identifying one or more nucleic acid molecules, comprising:

a) contacting at least one probe nucleic acid molecule with a survey population of nucleic acid molecules under conditions that promote hybridization between nucleic acid molecules to generate a probe-survey population mixture of nucleic acid molecules that comprises one or more probe nucleic acid molecules hybridized to one or more survey population nucleic acid molecules;

b) treating said probe-survey population mixture of nucleic acid molecules that comprises one or more probe nucleic acid molecules hybridized to one or more survey population nucleic acid molecules with a nucleolytic acitivity, such that nucleolytic activity-sensitive nucleic acid molecules are digested, to generate a population of nucleolytic activity-protected nucleic acid molecules;

c) amplifying said population of nucleolytic activity-protected nucleic acid molecules;

d) contacting said population of nucleolytic activity-protected nucleic acid molecules with a solid support comprising one or more attached nucleic acid molecules under conditions that promote hybridization between nucleic acid molecules to generate attached nucleic acid molecule/nucleolytic activity-protected nucleic acid molecule complexes; and

e) identifying one or more of said attached nucleic acid molecules or one or more of said nucleolytic activity-protected nucleic acid molecules in one or more attached nucleic acid molecule/nucleolytic activity-protected nucleic acid molecule complexes.

102. The method of claim 101, wherein said amplification uses a DNA polymerase or an RNA polymerase.

103. The method of claim 102, wherein said amplification uses a DNA polymerase.

104. The method of claim 103, wherein said DNA polymerase is DNA polymerase I, Klenow fragment, T.aquaticus polymerase, or T4 DNA polymerase.

105. The method of claim 102, wherein said amplification uses an RNA polymerase.

106. The method of claim 105, wherein said RNA polymerase is SP6 RNA polymerase or T7 RNA polymerase.

107. The method of claim 102, wherein said amplification is substantially linear.

108. A method of identifying one or more nucleic acid molecules, comprising:

a) contacting at least one probe nucleic acid molecule with a survey population of nucleic acid molecules under conditions that promote hybridization between nucleic acid molecules to generate a probe-survey population mixture of nucleic acid molecules that comprises one or more probe nucleic acid molecules hybridized to one or more survey population nucleic acid molecules;

b) treating said probe-survey population mixture of nucleic acid molecules that comprises one or more probe nucleic acid molecules hybridized to one or more survey population nucleic acid molecules with a nucleolytic activity, such that nucleolytic activity-sensitive nucleic acid molecules are digested, to generate a population of nucleolytic activity-protected nucleic acid molecules;

c) contacting said population of nucleolytic activity-protected nucleic acid molecules with a solid support comprising one or more attached nucleic acid molecules under conditions that promote hybridization between nucleic acid molecules to generate attached nucleic acid molecule/nucleolytic activity-protected nucleic acid molecule complexes; and

d) identifying one or more of said attached nucleic acid molecules or one or more of said nucleolytic activity-protected nucleic acid molecules in one or more attached nucleic acid molecule/nucleolytic activity-protected nucleic acid molecule complexes by labeling said attached nucleic acid molecule/nucleolytic activity-protected nucleic acid molecule complexes with at least one detectable label using at least one polymerase.

109. The method of claim 108, wherein said survey population comprises RNA.

110. The method of claim 108, wherein said survey population comprises DNA.

111. The method of claim 108, wherein said at least one probe comprises DNA.

112. The method of claim 108, wherein said nucleolytic activity comprises at least one nuclease.

113. The method of claim 112, wherein said at least one nuclease is a single-strand specific nuclease.

114. The method of claim 113, wherein said single-strand specific nuclease is S1 nuclease, Mung Bean nuclease, Rnase T1, RNAse A, or RNAse H.

115. The method of claim 108, wherein said solid support comprises glass, silicon, nylon, one or more polymers, one or more plastics, one or more ceramics, or one or more metals.

116. The method of claim 115, wherein said solid support is an array.

117. The method of claim 108, wherein said one or more attached nucleic acid molecules are at least partially complementary to said at least one probe nucleic acid molecule.

118. The method of claim 108, in which said at least one polymerase is one of the group comprising T4 DNA polymerase, T. aquaticus polymerase, Klenow fragment, DNA polymerase I, T7 RNA polymerase, SP6 RNA polymerase.

119. The method of claim 108, wherein said at least one detectable label comprises a radioisotope, a fluorochrome, an enzyme, or a specific binding member.

120. The method of claim 119, in which said at least one detectable label comprises at least one nucleotide.

121. The method of claim 120, wherein said at least one detectable label comprises at least two different nucleotides.